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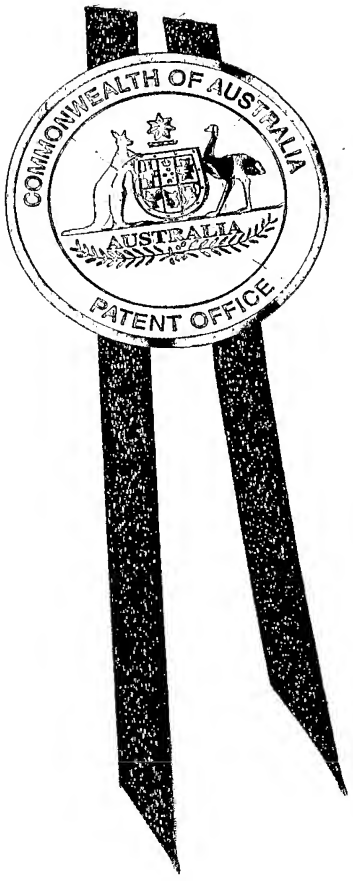

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USE OF AMINOSALICYLATES IN DIARRHOEA-PREDOMINANT IRRITABLE BOWEL SYNDROME

Technical Field

This invention relates to the production and use of therapeutic agents for treatment of diarrhoea-predominant Irritable Bowel Syndrome (IBS) – a condition known to arise from non-obvious causes. In particular, Irritable Bowel Syndrome which is defined as being a non-inflammatory bowel disease is also known not to be caused by detectable infection by a pathogenic organism or organisms. Irritable Bowel Syndrome is referred to as a non-specific bowel disorder and can be distinguished from infective and inflammatory bowel disease such as colitis or Crohn's disease on culture or histological grounds and endoscopic appearances.

Background Art

The large bowel in man and to a lesser extent the small bowel, contains large concentrations of various enteric bacteria. Generally, patients do not have pain, cramping, diarrhoea or constipation if the bacterial contents are not infected with pathogenic strains which may colonise the bowel and remain there for a prolonged periods of time. Acute infections and some chronic infections of the bowel flora can cause inflammatory changes in the lining. When inflammation is visible this condition is called Inflammatory Bowel Disease (IBD), which can be transient or long term – for example 'ulcerative colitis'. In some forms of IBD the visible inflammation is absent and can only be detected by taking a biopsy and finding histological changes of inflammation. In this case the pathologist terms the IBD as "microscopic colitis".

Where there are no visible colonoscopic or histological abnormalities in the colon and when the stool tests are negative for any known infection, and yet the patient continues to complain of symptoms referrable to the colon, such as urgency, diarrhoea, flatulence, cramping - the diagnosis of Irritable Bowel Syndrome can be made. Between 5% and 25% of the western population in different age groups may suffer from this disorder which has also been termed spastic colon, unstable colonic neurosis, spastic colitis or mucous colitis. In a classic case there is a triad of symptoms including low abdominal pain relieved by defaecation, alternating constipation/diarrhoea and the passage of small calibre stools. In some patients there may be accompanying watery diarrhoea with or without pain. Distension, flatulence, wind and at times nausea and headaches may be accompanying systemic symptoms.

The pathogenesis of IBS is unclear. Emotional disturbances, fibre deficiency, purgative abuse, food intolerance have been some of the implicated aetiological agents but none have been proven nor well demonstrated. Evidence for an infective cause or auto-immunity is lacking. Conventional treatments for IBS have been unsatisfactory as exemplified by the large number of therapies that have from time to time

be recommended or trialed. These have included psychotherapy, dietary regimens, anti-spasm agents, anti-cholinergics, anti-depressants, bulking agents, various receptor antagonists, carminatives, opiates, and tranquillisers – all without demonstrable success. Indeed there is no evidence that cure is possible. Yet IBS is one of the most common of the gastrointestinal illnesses and though not life-threatening causes great distress especially to those severely affected, and may bring a feeling of frustration and helplessness being generally lifelong. In particular, diarrhoea-predominant IBS can cause in some patients incontinence, inability of being sure that one can reach ones employment so causing some to drive from rest room to rest room on the way to work. In some patients urgency is so severe that they can only hold their motions for a few seconds, often leading to incontinence.

Borody described the use of 5-ASA compounds for the treatment of IBS (US Patent 5,519,014) but failed to note the more efficacious action of balsalazide for diarrhea-predominant IBS. Similarly, Lin et al (US Patent 6,326,364) discovered that 5-ASA compounds could inhibit clostridia, but did not appreciate that balsalazide with its unique side-chain had properties which can ameliorate diarrhea-predominant IBS in the absence of clostridia.

Disclosure of Invention

The present invention arose from the observations by the applicant that treatments of patients for other complaints with the standard 5ASA compounds such as mesalazine and olsalazine as well as 4ASA compounds were capable of suppressing symptoms in most patients with diarrhoea-predominant IBS. However, there was at his time no evidence that balsalazide can do the same, being a different and novel molecule. Balsalazide , molecular weight 437.32 (formula C17H13N3O6Na2.2H2O), is composed of 5-ASA joined to an unusually long chain, 4-amino benzoyl-β–alanine (4-ABA). The inventor noted that balsalzide can powerfully inhibit the symptoms of diarrhea in patients with diarrhea-predominant IBS, probably to a large extent due to the properties of the unique 'inactive carrier' side chain (4-ABA).Since discovering that balsalazide can inhibit even more powerfully the symptoms of diarrhea-predominant IBS than mesalazine (5-ASA), the present invention describes this unexpected finding. It is noted that the side chain together with the 5-ASA potentiates inhibition of gas production, cramping, fluid secretion, and mucus production.

Hence, the invention consists of a method of treatment of diarrhoea-predominant Irritable Bowel Syndrome and associated symptoms comprising a step of dosing a patient suffering therefrom with balsalazide. The second aspect of the invention consists of the balsalazide or its derivative used for treatment of non-specific bowel disorders, particularly diarrhoea-predominant IBS. The third aspect of the invention consists of the use of balsalazide in the manufacture of medicine with it as the base product with or without accompanying supportive or combination active and inactive agents.

The supportive combination agents may contain, among others, separate 5-ASA compounds, anti-cholinergics, probiotics (lactobacilli, bifibobacteria, clostridia eg Cllostridium butyricum, bacteroides, E coli and others), acceptable antibiotics (rifamycins eg rifabutin, rifampicin, refalazil, rifaximin and others; neomycin, vancomycin, tertracyclines), anti-spasm medications (eg dicyclomine), as well as various excipients.

The active ingredient may be incorporated with the pharmaceutically acceptable excipient/s in tablets, capsules or as powder in sachets. It may also be presented as granulated medication in larger volumes in sachets. The capsules, tablets or sachets may be taken one or more times per day in doses ranging from 100mg to 30grams per day. Agents can be enteric coated, may take the form of slow-release format to reach both the upper and lower bowel. Generally for long term therapy dosage will commence at a lower level and build up to the desired full amount over several weeks. The invention extends to multiple packages of individual dosages to be taken in sequence to provide such a gradual build up.

With the foregoing it will be appreciated that a new use has been discovered for balsalazide where previously no such effect has been described, and that actions of balsalazide can be further potentiated, even synergistically, by the addition of further agents.

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Nicolas Shortis..... Dated ...6.../...2.../ 2004